Project Details	
Project Code	MRC22NMHCa Rosser
Title	Analysing the differentiation and function of the neurons damaged in Huntington's Disease
Research Theme	Neuroscience & Mental Health
Summary	Striatal medium spiny neurons (MSNs) bear the brunt of pathology in Huntington's disease (HD). You will use a range of in vitro and in vivo cell, molecular genetic and whole animal techniques to dissect how the transcription factors FoxP1 and Mef2C function in MSNs differentiation. This knowledge is key for optimising MSN differentiation protocols from stem cells for disease modelling and cell therapies, and understanding the degeneration of MSNs in HD.
Description	Background: The striatum is the principal output nucleus of the basal ganglia and has critical roles in the control of movement, cognition and emotion. Degeneration of striatal Medium Spiny Neurons (MSNs) occurs early in Huntington's disease (HD), leading to progressive motor, cognitive and behavioural decline. Attempts to make MSNs from pluripotent stem cells (PSCs) for disease-modelling and cell therapy have seen modest success, but, to date, PSC-derived striatal neurons differ significantly from populations of "authentic" striatal cells. Producing MSNs that more closely resemble those generated in normal development requires better knowledge of the developmental processes that produce the normal range of adult MSN subtypes. We aim to advance this understanding by dissecting the function of two key transcription factors, FoxP1 and Mef2C, which our preliminary data suggest have distinct roles in MSN development. Such distinct roles would fit with known MSN heterogeneity and emphasise the importance of understanding how ALL cells of the striatum are made. This knowledge will aid optimisation of differentiation protocols for deriving MSNs from PSCs for disease modelling and cell therapies, and may aid understanding of why MSNs degenerate in HD. Work leading to this project: MSNs are the main striatal projection neuron, comprising approximately 90% of all striatal neurons, and are key for normal basal ganglia function. Although MSNs can be identified by a number of classic markers, they are not homogeneous and can be subdivided according to their co-transmitters, connections and whether they belong to patch or matrix subdivisions. In a microarray study we identified FoxP1 and Mef2c to be highly upregulated during peak MSN neurogenesis and have data suggesting their involvement in different, albeit overlapping, aspects of MSN differentiation. We reported that knock out (KO) of FoxP1 impaired MSN differentiation in vitro(1). We now have unpublished data demonstrating that striatal-specific KO of FoxP1 is associated with reduced striatal volume, loss of the key striatal markers DARPP-32 and CTIP2, and behavioural deficits. A similar striatal-specific KO of Mef2c results in a less dramatic reduction of striatal volume, along with loss of FoxP1 and DARPP-32, and a different profile of behavioural deficits. Aims: to (i) determine whether FoxP1 and Mef2c are involved in the differentiation of distinct subpopulations of MSNs, and (ii) initiate analysis of the mechanisms by which they affect MSN differentiation and function. Research plan: The project will provide a systematic comparative analysis of the function of the pivotal

	transcription factors FoxP1 and Mef2c on the differentiation of striatal cells using the mouse Cre-loxP system (using a Gsx2-Cre(2)) to produce striatal-specific conditional (CKO) of FoxP1 and Mef2c. These mice are validated and in use in our lab. Objectives are: (i) Characterise the striatal cell population of FoxP1 and Mef2c CKO mice compared to WT at different developmental stages and in culture, using a range of known striatal markers (e.g. FoxP1 and 2, Ctip2, DARPP-32, Helios, Ikaros) and glial markers. (ii) Quantify loss of MSNs from each of the patch and matrix compartments using a range of markers (e.g. MOR, substance P, met-enkephalin). (iii) Explore connectivity by combining markers with retrograde tracers to quantify striatal inputs and outputs. (iv) Characterise dendritic spine morphology in identifiable MSNs using Golgi cox combined with immunohistochemistry (our preliminary data indicate Mef2c striatal CKO leads to spine changes). (v) Determine the functional impact of FoxP1 and Mef2c CKO at a neural circuit level using whole-cell and multi-electrode array electrophysiological approaches in brain slices. Additional studies may include behavioural analysis and/or ScRNAseq (see Q 14). References: 1. Precious 2016 PMID:27154297, 2. Fogarty 2005 PMID:15790969
Supervisory Team	
Lead Supervisor	
Name	Professor Anne Rosser
Affiliation	Cardiff
College/Faculty	Biomedical and Life Sciences
Department/School	Medicine
Email Address	rosserae@cardiff.ac.uk
Co-Supervisor 1	
Name	Dr Michael Taylor
Affiliation	Cardiff
College/Faculty	Biomedical and Life Sciences
Department/School	Biosciences
Co-Supervisor 2	
Name	Dr Jonathan Brown
Affiliation	Exeter
College/Faculty	Medicine and Health
Department/School	Institute of Biomedical and Clinical Sciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	